

**IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF ARKANSAS
WESTERN DIVISION**

In re:	§	MDL Docket No. 4:03CV1507WRW
	§	
PREMPRO PRODUCTS LIABILITY	§	Reeves v. Wyeth, 4:05CV00163WRW
LITIGATION	§	Rush v. Wyeth, 4:05CV00497 WRW
	§	

**PLAINTIFFS' MEMORANDUM IN OPPOSITION TO
DEFENDANTS' MOTION TO EXCLUDE EXPERT TESTIMONY OF
DRS. KLIMBERG AND WALDRON AS TO SPECIFIC CAUSATION**

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I. INTRODUCTION

Defendants charge that medical science hasn't any idea what causes breast cancer. They view causation as a "riddle" because there is not yet any test kit or signature biomarker to diagnose their drug as the precise cause of plaintiffs' breast cancers. The riddle, however, is of defendants' own making. Defendants and their experts adhere to a distorted and myopic view of law and science. In a classic flat-earth fashion, defendants remain blind to the mainstream consensus in the medical community that combination hormone therapy ("CMHT") is a known cause of breast cancer. They turn their backs on differential diagnosis – a global methodology taught in medical school and practiced every day by clinicians in the real world – and denigrate Drs. Klimberg and Waldron as charlatans for using this technique.

Defendants also failed to do their homework on the legal standards for the admissibility of expert testimony for individual causation. The law is clear that doctors may base their individual diagnoses in large part on reliable epidemiological studies, as Drs. Klimberg and Waldron have done. The Eighth Circuit has endorsed this methodology and has also upheld differential diagnosis as a reliable technique because it is precisely how clinicians in their daily practice go about determining the likely etiology for their patients' cancers. Any conflicting views on the experts' conclusions are matters for the jury to decide. Accordingly, defendants' motion should be denied.

II. BACKGROUND

Drs. Klimberg and Waldron are highly respected physicians practicing in Little Rock. They have devoted much of their careers to the diagnosis and treatment of cancer. They have submitted Rule 26 reports on both general and specific causation. They are prepared to testify at trial in the *Reeves* and *Rush* cases that combination hormone therapy ("CMHT") can cause breast cancer in women, and that it was a substantial factor in causing the plaintiffs' breast cancers. Following is a synopsis of their opinions.

A. Dr. Klimberg's Causation Assessments.

Dr. Suzanne Klimberg is a breast surgical oncologist. She is the director of the breast cancer program at the Arkansas Cancer Research Center at University of Arkansas for Medical Sciences. She is also Director of the Fellowship in Diseases of the Breast. She has taught medical students for 15 years. She sees approximately 1,500 patients with breast disease every year and diagnoses more than 100 breast cancers annually. Dr. Klimberg is eminently qualified to testify on the causes of breast cancer generally and the specific cause of Ms. Reeves' and Ms. Rush's breast cancers.

On December 15, 2005, Dr. Klimberg submitted her Rule 26 expert report, which contained her opinion on general causation, i.e., that CMHT can cause breast cancer in some women.¹ In her report, she also described the methodology for determining the cause of cancer in an individual patient:

To make a causal assessment in an individual case, one would need to consider the totality of evidence, including statistical association, details about generally recognized and statistically significant risk factors, physiological response to the drugs, such as radiological evidence of changes in breast density before, during and after hormone therapy use, pathological biomarkers in breast tissue samples taken during biopsy and surgery, as well as duration of use of the hormone therapy drugs.²

On March 2, 2006, Dr. Klimberg submitted individual causation reports for Ms. Reeves and Ms. Rush.³ In both cases, Dr. Klimberg based her findings on the methodology and evidence described above.

1. Ms. Reeves

In her report, Dr. Klimberg noted that Ms. Reeves did not have several of the known risk factors for breast cancer: she had no family history of breast cancer; she did not drink; and she

¹ Ex. 01, Klimberg general causation report (Dec. 15, 2005)

² *Id.* at 7.

³ Ex. 02, Klimberg report on Reeves (Mar. 2, 2006); Ex. 03, Klimberg report on Rush (Mar. 2, 2006).

was not obese. Dr. Klimberg also considered other possible risk factors, including past smoking⁴ and use of oral contraceptives. Although Ms. Reeves had taken oral contraceptives for seven years, she quit using them at age 31 (approximately 29 years before her diagnosis of breast cancer). She also quit smoking in 1993. Dr. Klimberg also explained the Gail Model, a standard diagnostic tool she uses in her daily practice to calculate the baseline risk of breast cancer. The Gail Model is based in part on the amount of time the patient was exposed to estrogen, because the higher the level of estrogen receptor stimulation, the higher the risk of breast cancer. The Gail Model accounts for the presence – and absence – of risk factors. According to her Gail Model score, Ms. Reeves was not at high risk for breast cancer at the time she began taking CMHT.⁵ In addition, Ms. Reeves' breast density increased slightly over baseline after she began taking CMHT, whereas breast density normally decreases in postmenopausal women.⁶ Dr. Klimberg also considered the published literature on known breast cancer risk, including CMHT. Based on the totality of data, Dr. Klimberg ruled out the alternative causes and concluded that CMHT was the most likely contributing cause of Ms. Reeves' breast cancer.

2. Ms. Rush

In her report and review of Ms. Rush's medical history, Dr. Klimberg eliminated family history of breast cancer and alcohol use as a cause of Ms. Rush's breast cancer. Although Ms. Rush had a remote history of smoking (quit in 1984) and was borderline obese, Dr. Klimberg did

⁴ Cigarette smoking is not an established risk of breast cancer. *See Ex. 04, Klimberg dep. at 69:4-13 (Apr. 10, 2006).*

⁵ Ms. Reeves' Gail Model score was 1.1 at 5 years, and her lifetime risk at age 53 was 7.2. Dr. Klimberg found this risk to be low. *See Klimberg Report on Reeves* at p.4.

⁶ Dr. Klimberg was not able to view Ms. Reeves' mammography x-ray films before she submitted her expert report, but relied instead on the mammographer's reading, which noted a moderately increased density in Ms. Reeves' breast tissue. Later, Dr. Klimberg had an opportunity to view the films and disagreed with the mammographer's interpretation, and found that breast density was only minimally increased. However, because breast density typically decreases after menopause, the fact that Ms. Reeves' breasts maintained or slightly increased their density indicates that her breast tissue was more susceptible to the initiation and/or promotion of breast cancer caused by CMHT.

not consider these risk factors to be significant.⁷ According to her Gail Model score, Ms. Rush was not at high risk for breast cancer at the time she began using CMHT.⁸ Dr. Klimberg also noted that Ms. Rush experienced a slight increase in breast density after she began taking CMHT, which signaled an increase in proliferation of breast tissue and increased Type 1 lobular cells, which are at higher risk of carcinogenic mutation.⁹ Based on the totality of data, Dr. Klimberg accounted for the alternative causes and concluded that CMHT was the most likely contributing cause of Ms. Rush's breast cancer.

B. Dr. Waldron's Causation Assessments.

Dr. James Waldron is a diagnostic surgical pathologist at University of Arkansas for Medical Sciences (UAMS). He has also taught medical students as Professor of Pathology at UAMS for 17 years. In addition, he acts as a pathology consultant to medical institutions in Arkansas and the surrounding region. Dr. Waldron evaluates and interprets tissue samples for the purpose of diagnosing diseases. In any given year, Dr. Waldron studies and diagnoses over 5,000 surgical specimens. A significant portion of his daily experience includes analyzing breast tissue for the presence of cancer. He has written medical textbook chapters on breast pathology. Dr. Waldron is highly qualified to testify on the cause of breast cancer, both generally and in individual patients.

On December 15, Dr. Waldron submitted a Rule 26 report on breast cancer general causation.¹⁰ Dr. Waldron based his opinion on the wealth of statistical data showing that CMHT significantly increased the risk of breast cancer, as well as the "abundant scientific evidence

⁷ See Ex. 04, Klimberg dep. at 69:4-13 (smoking is not an established risk factor for breast cancer); Ex. 05, Klimberg dep. at 126:24-127:11 (overweight is only a modest risk factor).

⁸ Ms. Rush's Gail Model score was 1.5 at 5 years, and her lifetime risk at age 56 was 9.7.

⁹ Dr. Klimberg was not able to view the actual mammogram films for Ms. Rush before she submitted her report. However, later, when she had a chance to review the films, she did not agree with the mammographer's interpretation that Ms. Rush's breast density was significantly increased. She explained this discrepancy in her deposition at p. 28 (Ex. 06).

¹⁰ Ex. 07, Waldron general causation report (Dec. 15, 2005).

which supports the biological plausibility of a causal relationship, between CMHT and breast cancer.¹¹ He concluded, "there is an overwhelming body of evidence from epidemiological, experimental, and clinical studies indicating that CMHT can indeed cause breast cancer in some women."¹²

On February 16, 2006, Dr. Waldron submitted reports on individual causation for Ms. Reeves and Ms. Rush.¹³ Dr. Waldron based his findings on his training and experience as a surgical pathologist, the published medical literature on breast cancer and CMHT, a thorough review of the medical records, as well as his examination of tissue samples taken from both plaintiffs' breast cancers.

1. Ms. Reeves

In his report, Dr. Waldron described his examination of Ms. Reeves' breast tissue:

Carcinomas associated with hormone replacement therapy are predominantly estrogen and progesterone receptor positive. Most are either of lobular type or are well to moderately differentiated ductal carcinomas of the breast. My examination of the histologic material obtained from Linda Reeves shows her breast cancer to be a relatively well-differentiated ductal carcinoma, which was strongly positive for both estrogen receptor protein and progesterone receptor protein. These findings are consistent with the type of breast carcinoma induced and/or promoted by hormone replacement therapy.¹⁴

In addition, Dr. Waldron reviewed Ms. Reeves' medical records for risk factors that might otherwise contribute to her breast cancer. Finding that she had no significant risk factors, Dr. Waldron concluded that their absence further strengthened the probability (given the strong statistical data) that CMHT played a substantial role in initiating or promoting Ms. Reeves' breast cancer.

¹¹ *Id.* at 2.

¹² *Id.* at 3.

¹³ Ex. 08, Waldron report on Reeves (Feb. 16, 2009); Ex. 09, Waldron report on Rush (Feb. 16, 2009).

¹⁴ Waldron report on Reeves at 2-3.

2. Ms. Rush

In his report, Dr. Waldron set forth his analysis of Ms. Rush's breast tissue, which found her cancer to be a well-differentiated mammary ductal cell carcinoma. In addition, the tumor cells were strongly positive for both estrogen receptor protein and progesterone receptor protein. These findings were consistent with the type of breast cancer induced and/or promoted by CMHT. Dr. Waldron also reviewed Ms. Rush's medical records for other risk factors. Ms. Rush had no family history of breast cancer, and no history of prior benign breast disease or alcohol use. Although he noted that Ms. Rush had not given childbirth and was mildly obese, Dr. Waldron did not consider these risk factors significant. Dr. Waldron concluded that CMHT was a substantial factor in initiating or promoting Ms. Rush's breast cancer.

Defendants have filed a *Daubert* motion to preclude Drs. Klimberg and Waldron from testifying that CMHT was the likely cause of plaintiffs' breast cancer. Defendants base their argument primarily on clever sound bites and boilerplate incantations of their retained experts claiming that it is simply impossible to know what causes breast cancer. However, defendants ignore the large body of case law that explicitly permits experts to give opinions on individual causation in the absence of a signature biomarker or test, based on epidemiological data and other sources of evidence. These cases hold that expert opinions based on such evidence are valid and meet *Daubert's* threshold for reliability and relevance. Defendants' assertions are based on a distortion of law and science, as explained below. This motion should be denied.

III. LEGAL ARGUMENT

A. It is Well-Accepted in the Law and in the Medical Community that Cancer Can Be Diagnosed in an Individual Without the Need for a Definitive Biomarker.

At the outset, defendants and their retained experts insist that there is no such thing as individual causation when it comes to breast cancer. They contend that without a biochemical signature, it is impossible to diagnose the cause of cancer in any individual – even where solid epidemiological evidence supports the association. Defendants' position is incompatible with

the consensus in the medical community. For example, it is a given among physicians that cigarette smoking causes lung cancer, and that it is feasible to make that diagnosis in an individual patient even though there is no known "signature" disease to link smoking to lung tumors. One of Wyeth's own experts, Dr. David L. Page, Professor of Pathology and Preventative Medicine and Adjunct Professor of Pathology, agrees:

Q: Well, do you, do you agree that we know that cigarette smoking causes some lung cancers?

A: Yes.

Q: Can you say in an individual case that the cigarette smoking caused lung cancer?

A: To a high degree of likelihood, yes.

Q: What's that based on? What's the likelihood based on?

A: The likelihood is based on past experience and the reproducibility of that experience.

Q: Is there any signature in the biochemical sense, in a lung cancer, that allows you to say it was the cigarette smoke that did it as opposed to some other source?

A: I don't believe so.

Q: Is it then that it's just a matter of multiple observational studies that give you a statistical probability that the cigarette smoking was a cause of the lung cancer?

A: That's my opinion, yes.

Q: When you use the phrase "a cause of cancer," can you define for me what you mean by "cause"?

A: I thought we just did that. Our ability to understand causation of, um, malignant solid tumors depends on a likelihood analysis in every situation. It's not like a gunshot wound.

Q: So it's essentially based on epidemiological studies?

A: Well, it's it's – other elements are involved in the development of certainty, as I understand it. Biological plausibility, consistency of animal studies, although that's a secondary line of evidence, but the major one is the focus of epidemiological studies, whether they're observational or more recently interventional.

Ex. 10, Page dep. at 8-9 (Apr. 29, 2006).

The evidence here is directly analogous. Drs. Klimberg and Waldron base their diagnosis on the same factors articulated above by Dr. Page. Multiple epidemiological studies demonstrate that CMHT can cause or accelerate the growth of hormone-dependent tumors. This finding is not in dispute. Even defendants' causation experts do not deny it.¹⁵ As with cigarette smoking and lung cancer, there is not yet a signature finding or definitive biochemical test one can perform to prove with absolute certainty that a woman's breast cancer was caused by CMHT. However, as Drs. Klimberg and Waldron have done, a physician can make a reasonable diagnosis that CMHT was the likely cause of the plaintiffs' breast tumors based on multiple and confluent lines of reliable evidence, including epidemiological studies, biological plausibility, animal studies, pathology data, and the consideration of other known risk factors for breast cancer. This technique is a fundamental and well-accepted principle in law and medicine.

1. Epidemiological studies, alone or combined with other evidence, may be sufficient to establish individual causation.

The law reflects the understanding in toxic tort cases that substances known to produce cancer in the general population can be causally tied to the same cancer in an individual, even in the absence of signature biomarkers. Where multiple studies have shown a positive association between an agent and cancer – although not to the factor of 2.0 – the agent may be at least a producing factor in some types of cancers, even if the precise biological mechanism is not yet known. *Grassis v. Johns-Manville Corp.*, 591 A.2d 671, 675 (N.J. Super. Ct. 1991).

Where epidemiological evidence is available, most courts that have considered the issue have concluded that a plaintiff may present her case on individual causation to a jury if the epidemiological studies show at least a doubling of the risk of injury due to exposure to a toxic

¹⁵ See, e.g., Ex. 11 (Page dep. at 11-12).

agent (i.e., relative risk of 2.0 or greater).¹⁶ *Manko v. United States*, 636 F. Supp. 1419, 1434, 1437 (W.D. Mo. 1986), *aff'd in part*, 830 F.2d 831 (8th Cir. 1987); *Daubert v. Merrell Dow Pharmas., Inc.*, 43 F.3d 1311, 1320 (9th Cir. 1995); *DeLuca v. Merrell Dow Pharmas., Inc.*, 911 F.2d 941, 958-59 (3d Cir. 1990); *Landrigan v. Celotex Corp.*, 605 A.2d 1079, 1087 (N.J. 1992); *Merrell Dow Pharmas., Inc. v. Havner*, 953 S.W.2d 706, 717-18 (Tex. 1997).

Defendants' own experts acknowledge that strong epidemiological studies by themselves may be enough to establish individual causation. Dr. Hollingsworth, a surgeon, testified that although there is no magic threshold, epidemiological studies with a relative risk of above 3 was sufficient for him to infer causation in an individual case.¹⁷

However, even courts that have adopted the "doubling of risk" threshold also recognize that epidemiological findings that do not reach a relative risk of 2.0 may nevertheless be admissible to prove individual causation, if combined with other consistent evidence. *Daubert*, 43 F.3d at 1321; *Landrigan*, 605 A.2d. at 1087; *Havner*, 953 S.W.2d at 718-19. For example, if genetics can be ruled out in an individual's case, a relative risk greater than 1.5 may support an inference that the alleged toxin was more likely than not responsible for the plaintiff's disease. ANNOTATED REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (SECOND), p. 531 (2004).

As explained by the Second Circuit in *In re Joint Eastern & Southern Dist. Asbestos Litig.*, 52 F.3d 1124, 1128 (2d Cir. 1995), the plaintiff can meet her burden of individual causation either through studies conclusively establishing a relative risk of more than 2.0, or through epidemiological studies falling short of 2.0, combined with clinical or other evidence that strengthens the connection between the alleged toxin and plaintiff's disease. *Id.* Among the factors that strengthen the epidemiological findings are those found in the Bradford Hill "sufficiency criteria." *In re Asbestos*, 52 F.3d at 1128. These include: 1) strength of association;

¹⁶ A relative risk of 2.0 suggests a 50% likelihood that the agent caused the exposed individual's disease.

2) consistency; 3) specificity; 4) temporal relationship; 5) dose response; 6) biological plausibility; 7) coherence with existing knowledge; 8) cessation of exposure; and 9) replication of the findings. *REFERENCE MANUAL ON SCIENTIFIC EVIDENCE* at p. 517 (2004); *See also Havner*, 953 S.W.2d at 719 n.2. Although it is not necessary to meet all of these criteria, they are part of the sound and generally accepted methodology for making judgments about causation. *Havner*, 953 S.W.2d at 719.

The *Grassis* court succinctly described how an expert makes a reliable causal assessment of individual causation in a cancer case:

An epidemiologist cannot state that it is more likely than not that a particular case of colon cancer, after asbestos exposure, was caused by the asbestos. A medical doctor, however, or even one otherwise acquainted with the physiology of a particular patient and the progress of the disease, may make a medical judgment concerning the origin of a disease. The physician or other qualified expert may view the epidemiological studies and factor out other known risk factors such as family history, diet, alcohol consumption, smoking (surprisingly, generally recognized as not being a risk in colon cancer, according to the testimony in this case), or other factors which might enhance the remaining recognized risks, even though the risk in the study fell short of the 2.0 correlation.

Grassis, 591 A.2d at 675 (citations omitted).

This is the same methodology employed by Drs. Klimberg and Waldron when they developed their opinions that CMHT was the likely cause of Ms. Reeves' and Ms. Rush's breast cancer. Both experts reviewed the epidemiological studies on breast cancer and CMHT. They considered the plaintiffs' family histories, diet, alcohol consumption, weight, smoking (smoking is not a known risk factor for breast cancer) and CMHT use.

Drs. Waldron and Klimberg ruled out some of these known risk factors as alternative causes of the plaintiffs' cancer, and they found others to be small or less significant in relation to the risk of CMHT-induced breast cancer. Ultimately, based on the totality of data, they isolated CMHT as the likely cause. It is the same technique described by defense experts Page and

(Cont.)

¹⁷ Ex. 12, Hollingsworth dep at 85:18-86:14 and 115:9-116:4 (noting that a sole contributing cause of cancer could be based on a range of relative risks between 3 and 20).

Hollingsworth in determining how one goes about diagnosing cancer in the absence of a signature diagnostic test.

2. Epidemiological Studies relied upon by Drs. Klimberg and Waldron show that CMHT at least doubles the risk of all types of breast cancer in women.

Numerous case-case control and cohort epidemiological studies demonstrate that CMHT more than doubles the risk of breast cancer. At least 15 published studies reported statistically significant increases, with odds ratios greater than 2.0 for *all* types of breast cancer in women who took CMHT, and the risk increased with duration of use.¹⁸ Similarly, 15 epidemiological studies also show that CMHT causes at least a two-fold increased risk of hormone receptor positive tumors – the type of cancers suffered by Ms. Reeves and Ms. Rush.¹⁹ Eight studies measured the incidence of CMHT-induced ductal cancers, the histological subtype both plaintiffs had. All of the studies showed an increased risk.²⁰ Notably, the study published by Rosenberg and colleagues demonstrated that women exposed to the same dose of CMHT as the plaintiffs, and for longer than 5 years, had a 2.3 fold increased risk for ductal cancers. The Rosenberg study controlled for the known risk factors for cancer. And because a significant percentage of ductal cancers are not hormone-dependent (i.e., estrogen receptor or “ER negative”), combining the ER negative cancers with ER positive ductal cancers into one etiological mix underestimates the relative risk of true CMHT-fed ductal tumors.²¹

¹⁸ Appendix A-1 (CMHT studies on overall breast cancer rates)

¹⁹ Appendix A-2 (CMHT studies on ER+ breast cancers)

²⁰ Appendix A-3 (CMHT studies on ductal cancers)

²¹ T. Bagai & Shousha S., *Oestrogen receptor negativity as a marker for high-grade ductal carcinoma in situ of the breast*, 44, No. 5 HISTOPATHOLOGY 440-47 (May 2003); Li et al., *Clinical characteristics of different histologic types of breast cancer*, 93, No. 9 BRIT. J. CANCER 1046-52 (Oct. 31, 2005); A. Rody et al., *Estrogen receptor alpha and beta, progesterone receptor pS2 and HER-2/neu expression delineate different subgroups in ductal carcinoma in situ of the breast*. 12, No. 4 ONCOLOGY REP. 695-99 (Oct. 2004). See also REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, p. 509 n. 96 (2004) (quoting Rothman & Greenland: “Unwarranted assurances of a lack of any group effect can easily emerge from studies in which a wide range of etiologically unrelated outcomes are grouped.”)

What makes all of these studies so important is their relevance to this litigation: they were designed to investigate whether *combination* menopausal hormone therapy – the drug at issue in these bellwether cases – causes breast cancer. And many of these studies addressed the effect of CMHT on various subtypes of breast cancer, including hormone receptor positive tumors. The fact that CMHT also increases the risk of hormone-dependent breast cancers supports the likely mechanism that the drug feeds breast tumor growth.

Moreover, these data are reliable because they support the consensus in the medical community that CMHT is a known cause of breast cancer. For example, the International Agency for Research on Cancer (IARC) has concluded that, based on the same body of research, “[t]here is sufficient evidence in humans for the carcinogenicity of combined estrogen-progestogen menopausal therapy in the breast.”²² The American College of Obstetricians and Gynecologists (ACOG) recently stated: “There is ample evidence to support the conclusion that women who take HT are more likely to develop clinically evident breast cancer than women who do not take HT.”²³ In addition, the Third Edition of the textbook THE BREAST lists hormone replacement therapy as one of the “factors of proven significance” of increased risk of breast cancer.²⁴ Dr. Klimberg is the author of two chapters in this widely used medical text. Physicians rely on this knowledge in their daily clinical practice. Medical students are taught to include CMHT on their differential diagnosis list when considering the probable cause of breast cancer in their patients.

Overall, these epidemiological studies provide compelling evidence that CMHT was a substantial contributing cause of Ms. Reeves’ and Ms. Rush’s breast cancer. Drs. Klimberg and Waldron are entitled to rely on this data to support their conclusions.

²² IARC Monograph, No. 2, Section 5, 3rd draft, rev. 3 (May, 1995).

²³ American College of Obstetricians and Gynecologists, Women’s Health Care Physicians. *Breast Cancer*, 104 (4 Suppl.) OBSTetrics GYNECOLOGY 11S-16S (2004).

²⁴ V. Vogel, Ch. 16, “Epidemiology of Breast Cancer,” 341-354, 342, Table 16-1, in THE BREAST, 3d Ed. (K. Bland & E. Copeland, eds.) (2004).

3. Application of the Bradford Hill Criteria provides additional reliability to the epidemiological data relied on by Drs. Klimberg and Waldron.

The epidemiological data relied upon by Drs. Klimberg and Waldron are accorded even more strength based on the relevant “Bradford Hill” criteria. Accordingly, both experts reasonably relied upon these studies to support their conclusions that CMHT was the likely cause of the plaintiffs’ breast cancers.

Strength of association. As illustrated in Appendices A1 through A3, the epidemiology studies that measured the incidence of breast cancer in CMHT users found that the risk for all breast cancers was at least two times higher than in women who did not take CMHT, especially with long-term use.

Consistency. The results of the epidemiological studies on CMHT and breast cancer were consistent in their findings. As mentioned previously, the studies reported similar, statistically significant increases in risk of breast cancer with CMHT. This consistency reinforces the reliability of the studies.

Specificity. The studies shown in Appendix A specifically measured the effect of *combination* menopausal hormone therapy on breast cancer – the same drug regimen taken by plaintiffs. This is important, because defendants and their experts disregarded these CMHT findings and relied primarily on studies of estrogen therapy, not combination hormone therapy, and on studies whose endpoints did not specifically include breast cancer. Furthermore, the subjects in the CMHT studies shared characteristics similar to Ms. Reeves and Ms. Rush: all of the participants were women; the exposed groups took the same drug as plaintiffs, in the same dose, and many took it for several years. The subjects in the studies identified in Appendices A-2 and A-3 had the same breast cancer subtypes as both plaintiffs (estrogen-receptor positive and/or ductal tumors). Therefore, the studies directly apply to plaintiffs, which is a strong argument in favor of causation.

Temporal Relationship. Both plaintiffs and the study subjects in the “exposed” groups began taking CMHT before they developed cancer, not after. The horse preceded the cart. Thus, the data are reliable under this factor.

Dose Response. The studies show that risk of breast cancer from CMHT taken in a continuous dose (every day) formula was even higher than in users of the sequential (21-day) dose formulation, which is what Ms. Reeves and Ms. Rush took. In addition, the risk of breast cancer increases the longer women take either form of CMHT. Even some of defendants’ experts agree.²⁵ This evidence, often called “biological gradient,” supports CMHT’s drug effect.

Biological Plausibility/Cohherence with Existing Knowledge. The question this criterion poses is whether it makes sense for CMHT to cause breast cancer, based on existing knowledge, and whether the epidemiological data conflicts with other sources of evidence. The science on CMHT and its precise causal mechanism is still evolving. However, the entire medical community understands that if a breast tumor’s receptors are positive for estrogen and progesterone activity, it is a strong indication that estrogen and progestin fed the tumor’s growth. Even some of defendants’ experts agree that a plausible reason why CMHT causes breast cancer is its ability to increase cell proliferation rates.²⁶

Indeed, the two primary anti-cancer drugs used to treat hormone dependent breast cancer – tamoxifen and aromatase inhibitors – both work by slowing down or stopping the tumor from being fed by estrogen and progesterone: Tamoxifen attaches to the estrogen receptors (“ER+”) and turns them off. That, in turn, dramatically reduces the number of progesterone receptors (“PR+”). The aromatase inhibitors work by blocking the local production of estrogen in the fatty tissue of the breast. In either case, the hormones can no longer feed the tumor. As a result, the tumor withers and dies. This treatment is universal standard medical practice at every medical

²⁵ See, e.g., Ex. 13, Wesbrook dep. at 123:10-124:3.

²⁶ See, e.g., Ex. 14, Hollingsworth dep. 139:2-140:4.

institution, including the University of Arkansas for Medical Sciences. The theory of hormone-fed breast cancer is also globally accepted in the scientific community.

In addition, several studies demonstrate that CMHT increases epithelial cell proliferation in the breast.²⁷ In other words, the very cells in the breast where breast cancer almost always develops if being stimulated to divide, undergo mitosis. Estrogen in combination with progestin stimulates mitosis (cell division) mainly in the Terminal Duct Lobular Unit (“TDLU”), where most breast cancers originate.²⁸ Equally important, most small pre-existing lesions in the postmenopausal woman’s breast are highly estrogen-dependent for growth, as are many small early-stage tumors that would probably never increase in size unless they were fed by CMHT.²⁹

This proliferative effect is evident in women on CMHT: their breasts remain dense even after menopause (when density normally decreases); and in some women, breast density increases. Ms. Reeves and Ms. Rush both experienced maintained or increased breast density after they began taking CMHT. Most of these women experience a rapid *decrease* in breast density when they discontinue CMHT. This phenomenon is known as drug “dechallenge,” a test that most physicians consider as powerful evidence of drug effect.³⁰

Animal studies also support the “proliferation” mechanism of CMHT. For example, studies on female monkeys that had undergone surgically induced menopause and were then given CMHT developed much higher proliferation of breast tissue than monkeys that were not

²⁷ See, e.g., L.J. Hofseth et al., *Hormone Replacement Therapy with Estrogen or Estrogen Plus Medroxyprogesterone Acetate Is Associated with Increased Epithelial Proliferation in the Normal Postmenopausal Breast*, 86, No. 12, J. CLINICAL ENDOCRINOLOGY & METABOLISM, 4559 (1999).

²⁸ *Id.*

²⁹ See, e.g., D. Allred et al., *Histological and biological evolution of human premalignant breast disease*, 8 ENDOCRINE-RELATED CANCER 47-61 (2001).

³⁰ See Ernest Sterns & Benny Zee, *Mammographic Density Changes in Perimenopausal Women: Is Effect of Hormone Replacement Therapy Predictable?*, 59 BREAST CANCER RES. & TREATMENT 125 (2000).

given CMHT.³¹ Studies have also showed that CMHT has a proliferative effect on the breast tissue in mice.³² Wyeth's own internal animal studies showed that MPA (the progestin in Prempro and Provera) induced mammary tumors by proliferating cell growth.³³ The animal data are consistent with human studies, which explain a plausible mechanism for how the progestin component of CMHT can cause breast cancer. In fact, the leading textbook on pharmacology states:

"Both the WHI and [Million Women Study] data are thus consistent with earlier studies indicating that the progestin component (e.g., medroxyprogesterone) in hormone-replacement therapy plays a major role in this increased risk of breast cancer."

D. Loose and G. Stancel, Ch. 57, "Estrogens and Progestins," GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 11TH ED., 1541-1571, 1552 (McGraw-Hill 2006). And in his deposition, defense expert Kent Westbrook agreed that the addition of progestin to estrogen could play a significant role in the ability of CMHT to cause breast cancer.³⁴ Thus, the epidemiological studies on CMHT are coherent with existing animal and human data describing the proliferative effect of CMHT on postmenopausal breast tissue.

Cessation of exposure. As explained above, women who discontinue CMHT experience a decrease in breast density. These findings are consistent with epidemiological data on CMHT,

³¹ J.M. Cline et al., *Effects of hormone replacement therapy on the mammary gland of surgically postmenopausal cynomolgus macaques*, 171 AM. J. OBSTETRICS GYNECOLOGY. 93-100 (Jan. 1996); J.M. Cline et al., *Comparative effects of tibolone and conjugated equine estrogens with and without medroxyprogesterone acetate on the reproductive tract of female cynomolgus monkeys*, 9, No. 4 MENOPAUSE 242-252 (2002); J.M. Cline et al., *Effects of conjugated estrogens, medroxyprogesterone acetate, and tamoxifen on the mammary glands of macaques*, 48, No. 3 BREAST CANCER RES. & TREATMENT 221-29 (Apr. 1998).

³² A.M. Raafat et al., *Proliferative effects of combination estrogen and progesterone replacement therapy on the normal postmenopausal mammary gland in a murine model*, 184(3) AM. J. OBSTETRICS GYNECOLOGY. 340-49 (Feb. 2001); A.M. Raafat et al., *Estrogen and estrogen plus progestin act directly on the mammary gland to increase proliferation in a menopausal mouse model*, 187(1) J. CELL PHYSIOL. 81-89 (Apr. 2001).

³³ Ex. 15, W-MDL303-00000752, at 00000867-78 (NDA)

³⁴ Ex. 16, Westbrook dep., 124:4-124:14.

which show that the risk of breast cancer decreases after women discontinue CMHT.³⁵ This “dechallenge” is strong evidence of drug effect and adds reliable support to causation.

Replication of the findings. The published epidemiological studies relied upon by Drs. Klimberg and Waldron found a doubling or more of breast cancer risk in users of CMHT for periods of at least five years. The fact that over two dozen independently conducted studies have replicated and confirmed each of the others’ results is compelling evidence that the methodology employed was reliable.

In summary, Drs. Klimberg and Waldron determined that CMHT was the likely cause of plaintiffs’ breast cancers based in part on the large volume of epidemiological data demonstrating that CMHT causes hormone-dependent breast cancer in women, as well as other supporting sources of evidence published in the peer-reviewed literature. They also thoroughly reviewed the plaintiffs’ medical records, considered the other known risk factors, and eliminated all but CMHT as the probable cause of plaintiffs’ breast cancers. This methodology is generally accepted by the courts and the medical community, and is at least acknowledged by some of the defense experts as the appropriate way to make a judgment on causation in an individual case. Defendants are out of step with both mainstream science and the law when they contend that under *Daubert*, plaintiffs’ experts cannot prove that CMHT was the probable cause of plaintiffs’ breast cancer.

4. Differential diagnosis is a generally accepted method for assessing individual causation.

As discussed above, another factor in the determination of the admissibility of an expert’s opinion is the ability to rule out or account for alternative causes. *Lauzon v. Senco Products, Inc.*, 270 F.3d 681, 693 (8th Cir. 2001). Physicians frequently use this method, known as “differential

³⁵ L. Persson, *Cancer risk in women receiving estrogen-progestin replacement therapy*, 23, Suppl. S, MATURITIS 37-45 (May 1996); A. Tjønneland et al., *Hormone replacement therapy in relation to breast carcinoma incidence rate ratios*, 100, No. 11 CANCER 2328-37 (Jun. 1, 2004). See also Goodman & Gilman at 1552.

diagnoses." *Id.* at 693 n. 7. A reliable differential diagnosis is one that identifies the cause of the plaintiff's medical condition by eliminating other likely causes until the most probable cause is isolated. *Mattis v. Carlon Electrical Products*, 295 F.3d 856, 861 (8th Cir. 2002) (physician's testimony held reliable because she ruled out other likely causes and relied on published studies linking the toxin to plaintiff's injury). A medical opinion on causation, based on a proper differential diagnosis, is sufficiently reliable to satisfy the *Daubert* criteria. *Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1208 (8th Cir. 2000). Courts have overwhelmingly held that a reliable differential diagnosis is a valid foundation for an expert's opinion. *See Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 262-263 (4th Cir. 1999) (differential diagnosis is generally accepted in the medical community, has been subject to peer review and does not frequently lead to incorrect results).

A differential diagnosis is presumptively admissible. *Turner*, 229 F.3d at 1208. Moreover, an expert's opinion should not be excluded simply because he or she has failed to rule out *every* possible alternative cause. *Lauzon*, 270 F.3d at 693-94. The expert need only consider those other conceivable causes and explain why they were excluded. *Id.* at 694. Although it is common for medical experts to disagree on diagnosis and causation, questions of conflicting evidence must be left for the jury's determination. *Hose v. Chicago Northwestern Transportation Co.*, 70 F.3d 968, 976 (8th Cir. 1996). The doctor's explanations as to the existence of causes not ruled out go to the weight, not admissibility. *Lauzon*, 270 F.3d at 694; *see also Ambrosini v. Labarque*, 101 F.3d 129 (D.C. Cir. 1996) (holding that the existence of causes not eliminated pertains to weight, not admissibility).

Contrary to defendants' assertion, differential diagnosis is not only recognized and accepted in the Eighth Circuit as a valid and reliable methodology, it is what pathologists and clinicians do every day when they want to know what caused a patient's disease. As Dr. Waldron explained in his deposition, it was common in the course of giving surgical pathology conferences on breast cancer case to "go through the differential diagnosis of how we come up

with this kind of tumor rather than that kind of tumor. And we also review the literature regarding the etiology and risk associations of these tumors.”³⁶

When asked how he concluded that CMHT was a substantial factor in causing Ms. Reeves’ breast cancer, Dr. Waldron explained:

Q: What do you mean by “substantial factor in causing her breast carcinoma?”

A: Well, as we talked yesterday, my concept of causation includes promotion, aiding the tumor to progress at a faster rate than it otherwise would have, earlier than it might otherwise have, and/or manifesting when it might not have, had HRT not been given.

What I did was to ascertain that this was, in fact, one of the types of tumors that’s been – the relative risk of which is increased with combination hormone replacement therapy.

In other words, it’s a well-differentiated ductal carcinoma that’s strongly ER/PR positive. So it’s certainly the type of cancer which has been associated with an increased relative risk over ER/PR negative tumors, for instance.

And then I looked through her medical records to ascertain the potential impact of other contributors and found out that she doesn’t smoke or drink. She has no genetic or family history of breast cancer.

She has no previous biopsy that would show a background of proliferative breast disease. She did receive this therapy for well over eight years, so that puts her up into the higher end of the relative risk association range with hormone replacement therapy, and she has a normal [body] mass index of a normal range.

So that all of those factors being no contributors, nothing else that would set her apart from anyone else. The only factor in her case which sets her apart from anyone else is the fact that she has taken combination hormone replacement therapy for well over eight years, so that since we see an elevated relative risk in patients of that type, it’s reasonable to conclude that this was a factor in the causation of her particular neoplasm.³⁷

³⁶ Ex. 17, Waldron dep. at 37 (Apr. 18, 2006).

³⁷ Ex. 18, Waldron dep. at 60-61 (Apr. 18, 2006).

Similarly, Dr. Klimberg testified that she diagnosed CMHT as a substantial contributing factor in causing plaintiffs' breast cancer by looking at all of the contributing factors and finding the most likely one, based on the totality of the medical records and available data.³⁸

The differential diagnoses completed by Drs. Klimberg and Waldron meet the legal requirements for reliability. These physicians accounted for all of the known alternative causes of breast cancer and explained how they ruled them out. The law does not require this exercise to be carried to a quixotic extreme. *Lauzon*, 270 F.3d at 693. Any dispute over the doctors' explanations as to factors not ruled in or out is a question for the jury to decide. If defendants want to attack plaintiffs' experts' conclusions, they may do so through cross-examination.

B. Defendants' Various Attacks on Drs. Klimberg and Waldron Are Frivolous.

Throughout their motion, defendants make petty and unwarranted criticisms of Drs. Klimberg and Waldron in an effort to discredit them before the Court. Following are just a few illustrations of defendants' fondness for impugning opposing experts.

1. "Lack of Publications."

Defendants take Dr. Klimberg to task for "not even attempting" to publish her opinions on CMHT – as if that were grounds for disqualifying her as an expert.³⁹ Defendants chose not to inform the Court that Dr. Klimberg is in the process of preparing a paper for publication regarding hormones and breast cancer. One of Dr. Klimberg's co-authors on the paper is Dr. Westbrook, who has been hired by defendants in this litigation to discredit her opinions on causation.⁴⁰ Nor did defendants mention that Dr. Klimberg has published chapters in textbooks on causes of breast cancer.⁴¹ Plaintiffs are unaware of any opinions published prior to litigation by Drs. Hollingsworth or other defense experts, that CMHT does not cause breast cancer.

³⁸ See Ex. 19, Klimberg dep. at 292-93 (April 10, 2006); see also Ex. 01, Klimberg general causation report at 7, second to last page.

³⁹ Def. Br. at 4.

⁴⁰ Ex. 20, Klimberg dep at 99-100 (Apr. 10, 2006).

2. “Expert Report Not Objective.”

Defendants also attack Dr. Klimberg’s report, alleging that it was “dashed off in a 24-hour period,” dismissing it as “slipshod” and lacking in objectivity. This accusation is false, and it blatantly mischaracterizes of Dr. Klimberg’s testimony. In her deposition, Dr. Klimberg described in detail the lengthy process of how she developed the outline and content for her report, well in advance of the report deadline. It took her 24 hours to revise her draft report into final form, which she typed herself.⁴² She did not, as defendants would have this Court believe, develop her opinions at the last minute.

Defendants use deceptive sound bites to suggest that Dr. Klimberg did not adhere to “peer review” standards for objectivity in drafting her report. Def. Br. at 5. Conveniently, defendants omitted the relevant part of her testimony:

Q: But the truth of the matter is, this paper, your report on combination therapy and breast cancer is not the same type of paper that you would submit for peer review. Isn’t that true?

A: No, that’s not true. There are several types of peer review that you go through, and I am an editor on multiple scientific publications. And you are asking for my professional opinion, and there’s editorials that do just that. And this is the type of paper that I view that is. And this is the type of thing that you can do.

Q: So this is –

A: I don’t think that this is at all inconsistent. It’s not a peer reviewed randomized study or an animal study in which you would – you still make your case, but you would bring in other opposing arguments of why your case is still true.

Q: And this is, then – you put this together to support the opinion that you were going to express in this litigation. Is that correct?

A: I was asked to – express my professional opinion.

Q: And then you pulled together articles that you felt supported that opinion. Is that correct?

(Cont.)
⁴¹ Ex. 20, Klimberg dep at 100 (Apr. 10, 2006).

⁴² Ex. 21, Klimberg dep at 90-98 (Apr. 10, 2006).

A: Yes, that would be my – the way you look at the totality of the evidence for and against, and you want to express why given a short amount of time and paper, that you express that you want to make your case.

Ex. 22, Klimberg dep. at 279-281. As Dr. Klimberg explained, she analyzed the data as she would as part of her daily work; only the format and purpose are different. Dr. Klimberg is not a professional expert. She should not be faulted for her efforts to write – and type – the report herself and comply with what she understood to be legally required for its submission.

Defendants failed to disclose that both Drs. Klimberg and Waldron developed their opinions that CMHT were a known cause of breast cancer independent of litigation. Here is what Dr. Waldron had to say:

Q: Prior to being hired by plaintiffs in this case, have you ever experienced the opinion that hormone replacement therapy causes breast cancer in a lecture?

A: Yes, I think – I think I have. We commonly, in the course of doing surgical pathology conferences, certainly given – I couldn't tell you how many surgical path conferences I have given on breast cancer cases. Certainly in the context of those cases, we go through the differential diagnosis of how we come up with this tumor rather than that kind of tumor. And we also review the literature regarding etiology and risk associations of these tumors. And in the course of those conferences, hormone therapy association would have come up.

Also, my own – my own wife, who is of an age in which this is a consideration, had questions that several years ago, I began looking at to answer her questions. So I had a personal interest in this topic as well that I reviewed – have reviewed papers on.

Q: Okay. Have you ever put your opinions regarding this in writing?

A: I don't think so, no.⁴³

Dr. Klimberg testified that she believed CMHT caused breast cancer since she began her clinical practice in 1990.⁴⁴ These busy physicians may not have had time to publish every

⁴³ Ex. 23, Waldron dep. at 37-38 (Apr. 18, 2006).

⁴⁴ Ex. 24, Klimberg dep. at 324.

opinion they had outside of litigation, but long ago, they warned their spouses and patients that CMHT could cause breast cancer.

Defendants and their experts are reminded that they dwell in glass houses. Many of the defense experts developed their opinions solely for litigation and have been handsomely paid. Their reports – some of which were written (and typed, and spell-checked) by defense lawyers – are arguably inadequate, and devoid of balanced references to the large volume of epidemiology that runs counter to their opinions.⁴⁵ Perceived bias and honest disagreement on causation fall outside *Daubert's* ambit; they are matters for the jury to decide. If defendants wish to challenge the credibility and integrity of Drs. Klimberg and Waldron, they are free to cross-examine them at trial. However, underhanded and vitriolic attacks of the sort aimed at these well-qualified experts serve no purpose here.

III. CONCLUSION

For the reasons stated above, the Court should deny defendants' motion.

DATED: June 29, 2006.

Respectfully submitted,

By: /s/ Leslie W. O'Leary

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⁴⁵ For example, the reports submitted by Drs. Hollingsworth and Westbrook – the defense expert counterparts to Drs. Klimberg and Waldron – were each barely over one page in length. They consisted of summary opinions without any scientific foundation.

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APPENDIX A

APPENDIX A-1 CMHT STUDIES SHOWING A DOUBLING OR MORE RELATIVE RISK ALL CANCER SUBTYPES		
Author/Date	Length of Use	Relative Risk or Odds Ratio
Persson (1997)	Over 10 years	2.6
Magnusson (1999)	5+ Years Current Use	2.68
	10+ Years Ever Use	2.43
Gapstur (1999)	Over 5 years	2.65
Kirsh (2002)	Over 10 years	3.48
Jernstrom (2003)	Varied: Ever Use vs Never Use	3.3
Olsson (2003)	1-48 Months Sequential	2.53
Li (2003)	Over 5 years Current Use	2.1
	Over 15 years Ever Use	2.9
MWS (2003)	Any Duration/Current Use	2.0
Stahlberg (2004)	Any Duration/Current Use, Incl. Estrogen Only	2.74
	Any Duration/Current Use, Sequential Combo	3.3
Holmberg (2004)	Any Duration (HABIT study - halted)	3.5
Tjønneland (2004)	Ever Use vs Never Use	2.22
Bakken (2004)	Over 5 Years Sequential	2.2
Stahlberg (2005)	Any Duration/Current Use	2.42
Lee (2006)	5-10 Years	2.07
	10 or More Years	2.73
Li (2006)	Over 5 Years	2.2

APPENDIX A-2
CMHT STUDIES SHOWING A DOUBLING OR MORE RISK FOR
HORMONE RECEPTOR POSITIVE TUMORS

Author/Date	Length of Use	Relative Risk or Odds Ratio
Persson (1997)	Over 10 years	2.6
Magnusson (1999)	5+ Years Current Use	2.68
	10+ Years Ever Use	2.43
Gapstur (1999)	Over 5 years	2.65
Kirsh (2002)	Over 10 years	3.48
Jernstrom (2003)	Varied: Ever Use vs Never Use	3.3
Olsson (2003)	Sequential 1-48 months	2.53
Li (2003)	Over 5 years Current Use	2.1
	Over 15 years Ever Use	2.9
MWS (2003)	Any Duration/Current Use	2.0
Stahlberg (2004)	Any Duration/Current Use, Incl. Estrogen Only	2.74
	Any Duration/Current Use, Sequential Combo	3.3
Holmberg (2004)	Any Duration (HABIT study - halted)	3.5
Tjønneland (2004)	Ever Use vs Never Use	2.22
Bakken (2004)	Over 5 Years Sequential	2.2
Stahlberg (2005)	Any Duration/Current Use	2.42
Lee (2006)	5-10 Years	2.07
	10 or More Years	2.73
Li (2006)	Over 5 Years	2.2

APPENDIX A-3
CMHT STUDIES SHOWING ANY INCREASED RISK FOR
DUCTAL TUMORS
(Combines ER+ and ER- Subtypes)

Author/Date	Length of Use	Relative Risk or Odds Ratio
Ursin (2002)	5 to 10 Years	1.52
	Over 10 Years	1.65
Kerlikowske (2003)	Over 5 Years	1.41
Li (2003)	Any Duration – Sequential	1.7
	Current Use Sequential	2.0
Tjønneland (2004)	Ever Use	2.1
Stahlberg (2004)	Ever Use – Sequential	3.10
Lee (2006)	Ever Use vs Never Use	1.3
Rosenberg (2006)	Over 5 Years – Sequential	2.3
Li (May 2006)	Any Duration Current Use	1.2

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing document was served according to this Court's provision for service as set forth in the pretrial orders and sent to the following counsel of record as indicated below on this 29th day of June, 2006.

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EXHIBIT LIST

Exhibit 1.	Klimberg general causation report (Dec. 15, 2005)	
Exhibit 2.	Klimberg report on Reeves (Mar. 2, 2006)	
Exhibit 3.	Klimberg report on Rush (Mar. 2, 2006)	
Exhibit 4.	Klimberg dep. at 69 (Apr. 10, 2006)	
Exhibit 5.	Klimberg dep. at 126-127 (Apr. 10, 2006)	
Exhibit 6.	Klimberg dep. at 28 (Apr. 10, 2006)	
Exhibit 7.	Waldron general causation report (Dec. 15, 2005)	
Exhibit 8.	Waldron report on Reeves (Feb. 16, 2006)	
Exhibit 9.	Waldron report on Rush (Feb. 16, 2006)	
Exhibit 10.	David L. Page dep. at 8-9 (Apr. 29, 2006)	
Exhibit 11.	David L. Page dep. at 11-12 (Apr. 29, 2006)	
Exhibit 12.	Hollingsworth dep. at 85-86, and 115-116 (June 1, 2006)	
Exhibit 13.	Wesbrook dep. at 123-124 (June 8, 2006)	
Exhibit 14.	Hollingsworth dep. 139-140 (June 1, 2006)	
Exhibit 15.	W-MDL303-00000752, at 00000867-78 (NDA)	SCO*
Exhibit 16.	Westbrook dep., 124 (June 8, 2006)	
Exhibit 17.	Waldron dep. at 37 (Apr. 18, 2006)	
Exhibit 18.	Waldron dep. at 60-61 (Apr. 18, 2006)	
Exhibit 19.	Klimberg dep. at 292-93 (April 10, 2006)	
Exhibit 20.	Klimberg dep at 99-100 (Apr. 10, 2006)	
Exhibit 21.	Klimberg dep at 90-98 (Apr. 10, 2006)	
Exhibit 22.	Klimberg dep. at 279-281 (Apr. 10, 2006)	
Exhibit 23.	Waldron dep. at 37-38 (Apr. 18, 2006)	
Exhibit 24.	Klimberg dep. at 324 (Apr. 10, 2006)	

* Subject to Confidentiality Order (Filed Under Separate Cover)